Title

Stress, Allostatic load and periodontal diseases

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Abstract

Psychosocial stress plays an important role in periodontal disease through biological and behavioural pathways. In this paper we reviewed studies that examined the relationship between stress and periodontal diseases, and different measures used to assess stress. Self-reported measures such as Perceived Stress Scale (PSS) and Stress Appraisal Measure (SAM) have been traditionally used to assess stress. Frequent and repeated exposure to stressor lead to wear and tear of the body system resulting in what is known as Allostatic load. In recent years few studies examining the relationship between stress and periodontal diseases have used an aggregate variable including primary and secondary markers of Allostatic load as a biological marker of stress. While research on the relationship between Allostatic load and periodontal disease is still developing, as most of the studies used cross-sectional data, this line of research presents a good opportunity for establishing a composite biological indicator as a risk factors for periodontal disease. It is will also be potentially beneficial for personalised periodontics as it will help altering intervention to specific levels of risk, and will help in integrating oral and general health promotion policies.

Introduction:

Psychological stress has been postulated as a risk factor for a number of chronic health conditions such as cardiovascular diseases, diabetes and obesity among others (23, 32, 58, 57). Stresses induced by poverty, unemployment, job insecurity, highly demanding routine jobs and lack of control at the work place and at home have been linked to cardiovascular diseases, obesity, diabetes, physical limitations and cancer (28, 71). The vicious cycle between socioeconomic factors, stress and health has perhaps been best described by Evans and colleague (14) as 'poverty gets under the skin'. Stress affects health through different pathways which include biological impact on autoimmune system, endocrine and metabolisms (43). Stress can also affect health through changes in behaviours. Individuals may adopt some unhealthy behaviours such as smoking, excessive drinking and use of illicit drugs to cope with stressful situations (33). There is also evidence that stress affects oral health (19). Unhealthy behaviours used as a coping mechanism with stresses such as smoking, drinking and comfort eating are all risk factors to periodontal diseases, dental caries and oral cancer (19). Additionally, biological changes associated with stresses are also depicted as risk factor for oral diseases (76). There is also evidence that stresses are linked to salivary changes which increases susceptibility to dental caries (4). On the other hand, the biological pathways between stresses and periodontal diseases appear to be more evident and have been addressed in several studies (3, 59, 76). Chronic and repeated exposures to stressors affect periodontal tissues in the same manner they affect other body systems (59).

Recent studies on the global burden of oral health have suggested that the prevalence of periodontal diseases is increasing (39), contradictory to a previous review (52). Furthermore, periodontal diseases appear to have an increasing impact on disability-adjusted life year (DALY) (31). Several reviews have addressed proximal risk factors for periodontal diseases highlighting opportunities to clinically tackle the burden of the disease (72). Fewer reviews have addressed the role of stress and psychological wellbeing on periodontal disease (19, 76). Studies have also examined the mediating role of stress between socioeconomic position and periodontal diseases (19, 59). While identifying the relationship between stress and periodontal diseases might help identifying those at high risk for timely intervention, its main importance lies in highlighting the role of environmental and social factors which could only be addressed at a higher level.

Given the increasing global burden of periodontal diseases, and the importance of the stress as a modifiable risk factor for periodontal diseases along with other chronic conditions, we conducted this narrative review pertaining to the role of stress in periodontal diseases and the different mechanisms through which stress impacts periodontal diseases.

The role of stress in the complex determinants of periodontal disease

Periodontal disease is a socially patterned condition with a strong behavioural component. Smoking and poor oral hygiene associated with inadequate personal and professional tooth cleaning are among the top behavioural risk factors for periodontal disease (66, 72). There is also a strong genetic component that increases susceptibility to the disease (11). Certain systemic conditions are also implicated in predisposing individuals to periodontitis, these include diabetes, leukaemia, acquired neutropenia among others (66). Psychological stressors were repeatedly shown to play an important role in periodontitis as they could influence the behavioural risk factors for periodontitis or/ and affect periodontal tissues directly. Studies have shown that individuals under stresses are more likely to smoke, less likely to brush their teeth and less likely to visit a dentist (33, 40), all-important behavioural determinants of periodontal diseases. On the other hand, studies have shown that stressors impact on the body

system increasing susceptibility to inflammation and impacting on the host response and endocrine systems (42, 43, 64). Such reactions to chronic stressors impact different body tissues including periodontium along with other tissues. Unsurprisingly, the common effect of stressors on different body organs was implicated in the relationship between systemic conditions and periodontal diseases (3, 59). Finally, examining the contextual determinants of health and related-behaviours will enable identifying socioeconomic and environmental factors which impact on both stress and behaviours directly by limiting individual's ability to engage in healthy behaviours and avoid unhealthy ones, and indirectly through psychological pathways, which include stress (43).

Types of psychosocial stresses

Psychosocial stress can be defined as the physiological and psychological changes that occur in the body when an external demand or stressor taxes an individual's adaptive capacity (9). Based on the exposure times, it can be broadly classified as chronic or acute forms, however, there is no universally accepted definitions or established temporal cut-off periods for acute and chronic stress.

Stressor are external stimuli that cause stress in an individual and they are grouped into three groups: (**a) Disasters or crisis.** An unpredictable event which is completely out of the control of the individual. For instance, devastating natural disasters such as major floods or earthquakes, or wars, etc. **(b) Major life events**. These are rare events that can be either positive or negative and include marital separation, imprisonment, death of a close family member, dismissal from work, personal injury and so on. **(c) Micro stressors**. Accumulation of micro stressors or daily hassles can have the same negative impact on our health as experiencing a major stressful event. They occur in every individual's life, however they are different for each individual, as not everyone perceives a certain event as stressful (53).

Acute stressors are most commonly referred to as short-term and time-limited events, while chronic stressors denote conditions which are longer lasting and may not be attributed to a discrete event (25).

The organisational model of the stress process that explains how chronic stress leads to deleterious health outcomes can be categorised into three broad stages: exposure to environmental demands or negative life events or stressors, self- evaluation and appraisal of the stressors which could elicit negative responses in the absence of coping skills and activation of the biological system in response to environmental and psychological demand (10, 24). This conceptualisation of stress serves as a resource for developing stress assessment tools to aid researchers to select an appropriate measure to use in different studies.

Stress assessment

There are several subjective, objective and physiological/biomedical measures to measure stress responses. In the absence of a gold standard for measurement of stress, selection of tool depends on the stressor (acute or chronic) that is presented to the study subjects, the methodological constraints of study design, and the research question (1). Questionnaires and interviews are the main measurement tools to assess the environmental and self-perceived stress, while biomarkers or endocrine measures help to quantify physiological or chronic stress (64). In this section, the most widely used measures of stress will be discussed.

Self-reported measures

Perceived Stress Scale (PSS): The most validated tool with strong psychometric properties, comprising of 14-items that rate the stress based on the frequency of difficult events in a period of one month. Other two short versions of the PSS scale are PSS-4 and PSS-10. Since perceived

stress has a large impact on cortisol level, PSS scores tend to be positively correlated with biomarkers of stress (8).

Stress Appraisal Measure (SAM): This pooled inventory of 28 items is developed based on the different aspects of six dimensions of primary appraisal (threat, challenge, and centrality) and secondary appraisal (controllable-by-self, controllable-by- others, uncontrollable-by-anyone) of stress. On a four-point scale, each item is rated and an overall mean rating is obtained (50).

Impact of Event Scale (IES): The IES-R consists of 22 items and assesses the degree to which a distressful traumatic event impacts an individual. An individual is required to identify a difficult situation in the past week and indicate the difficulty score in a 5-point scale ranging from "not at all" to "extremely", yielding a total score up to 88 (77)**.**

Life Experiences Survey (LES): The Life Experiences Survey is a 60-item self-reported structured interview which includes events that typically would be perceived as negative or positive. If individuals had experienced the event, they were asked to indicate, on a 7-point scale, the extent to which it had an impact Typically, the range span from extremely negative to no influence to extremely positive scores (60).

Apart from these, there are many other self-report instruments and structured interviews (Table 1). The appropriate assessment of stress is critical to an understanding of the potential consequences of these disorders as well as the development of appropriate behavioural and pharmacological treatments. The reliability and validity of screening instruments must be carefully evaluated before using them.

Clinical-biochemical measures

(a) Neuroendocrine biomarkers

Whenever a stressor induces chronic physiological stress, there are some system level alterations as well as energy production to maintain homeostasis. The neuroendocrine system is the first to be triggered and this will initiate the release endocrine markers which can be effectively detected. The various neuroendocrine biomarkers of chronic stress currently in use include Cortisol, Dehydroepiandrosterone (DHEA), Adrenaline, Noradrenaline and Dopamine.

Cortisol and DHEA: Cortisol is one of the most frequently used measures to quantify physiological stress. As a mediator of many secondary outcomes, it captures the status of hypothalamic–pituitary–adrenal (HPA) axis functioning. The instantaneous sources of cortisol can be blood (plasma or serum) and saliva. DHEA is also a marker of chronic stress and functions as an HPA antagonist. DHEA measurements directly capture the status of HPA axis functioning. However, due to the large diurnal variation in cortisol or DHEA levels which make it difficult to ascertain the levels from a single measurement, it is not generally effective as a biomarker for chronic stress.

In recent years, researchers have also become increasingly interested in another potentially practical mode of assessing the cumulative exposure of stress from hair sample. Unlike, other less reliable measures, this non-invasive sample has several advantages in terms of collection, storage and transportation (69, 70). Furthermore, it can also reflect both acute and chronic stress.

Adrenaline, Dopamine, Aldosterone and Noradrenaline:

These biomarkers consistently respond to stress regardless of whether it is perceived as a threat or as an opportunity for gain. Hence, these measures may not be necessarily the static measures of stress (22, 47). Nevertheless, when used in conjunction with other markers of chronic stress in an allostatic load model, noradrenaline and dopamine can be one of the useful pointers of sympathetic nervous system and cardiovascular functioning, respectively. Apart from this, the

aldosterone can be a useful measure of the functioning of the adrenal gland when used in conjunction with other biomarkers of allostatic load (46). Importantly, it is the frequency of acute stressors that are detrimental to health.

(b) Immunological biomarkers

Another commonly used biomarker of chronic stress is circulating levels of Interleukin-6 (IL-6), Tumour necrotic factor-α (TNF-α), C-Reactive Protein (CRP), and Insulin-like growth factor (IGF-1) (34, 48). The secretion of immunological biomarkers could be altered by the chronic exposure to stress. Interleukin-6, a pro-inflammatory cytokine which works synergistically with Tumour necrotic factor-α and IL-1 can indirectly capture the dysfunction of the HPA axis mediated by glucocorticoid signalling. CRP levels has been used in many studies as one of the inflammatory responses to chronic stress (73).

These biomarkers, however, are markers of inflammation, and are not used as primary markers of stress. They are rather indicators of how stress can affect the immune system. Although they were used with other primary markers such as adrenaline and cortisol to test the relationship between stress and cardiovascular and periodontal diseases (43, 59, 64, 78), they could also be found in the body system in as markers of inflammation in the absence of stress.

(c) Metabolic biomarkers

Changes in metabolism have also been used as secondary and tertiary markers of stress (42, 44, 64). Studies have used biomarkers such as cholesterol levels, Albumin, Waist-Hip ratio and Glycosylated haemoglobin in combination with other biomarkers discussed above. They are however majorly confounded by many variables which make them less reliable and valid measure in epidemiological studies.

(d) Allostatic Load

No single metric can accurately measure chronic stress and this shortcoming is managed by using a compendium of biomarkers released from different bodily system known as Allostatic load, which is generally defined as the "the price the body pays for being forced to adapt to adverse psychological or physical situations, and it represents either the presence of too much stress, or the inefficient operation of the stress hormone response system" (42).

Allostasis is an active physiological or biochemical adaptation that helps the body get back to re-establishing homeostasis after exposure to a stressor. While the acute stress response is critical for survival, repeated or chronic exposure to stressors can have deleterious effects on the nervous, endocrine and immune functions. When individuals are repeatedly exposed to chronic stressors biological responses are induced to cope with these stressors, leading to wear and tear on the immune, cardiovascular, metabolic and nervous systems and is primarily marked by elevated adrenaline and cortisol levels in the body, a phenomenon known as allostatic load (42, 44, 64, 78).

Since chronic exposure to stress hinders the normal functioning of the physiological regulatory system, the status of the biological system should be considered for allostatic load measurement. The first study to validate these interlinking. The cascading relationships were validated initially by the McArthur successful Aging Study (43, 64). It contained information about the 10 parameters which determine the physiological status of the HPA axis, sympathetic nervous system, metabolic processes and cardiovascular system. The first four primary mediators pertaining to stress response were DHEA, cortisol, adrenaline and noradrenaline. Other mediators were indices of outcomes; metabolic (e.g. insulin, glucose, total cholesterol, high density lipoprotein, cholesterol, triglycerides, visceral fat depositing), cardiovascular (e.g., systolic and diastolic blood pressure), and immune, e.g., Fibrinogen, C-reactive protein

(CRP) (Table 2). Most of the biomarkers measured to derive the allostatic load score are biologically interconnected. Although allostatic load reflects cumulative exposures to stress over many years, most allostatic load studies are of cross sectional nature. Longitudinal measurement of allostatic load can give information about the allostatic profile of an individual at various stages of developing stress-related health outcomes. This can shed some insight into the pathways of pathophysiology leading to the development of disease (36, 44, 43).

Stress pathways to periodontal diseases

(a) Biological changes

In response to chronic stressors, a cascade of reactions occurs. First, the hypothalamus releases corticotropin-releasing hormone (CRH) from the periventricular nucleus, initiating the HPA pathway, which in turn stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). Because of the stimulating effect of circulating ACTH glucocorticoids such as cortisol (primary stress hormone) is produced by the cortex of the adrenal glands. DHEA, an endogenous, cortisol regulatory hormone is also released. Another parallel pathway, sympatho-adrenal medullary (SAM) axis also operates at the same time in the medullary cortex of adrenal gland, resulting in the release of adrenaline and nor-adrenaline (together called catecholamines) (18, 63)

Glucocorticoids, including cortisol, exert major suppressive effects through highly specific mechanisms at different levels. At the molecular level, they inhibit vital functions of inflammatory cells including macrophages, neutrophils, eosinophils, and mast cells in functions such as Chemotaxis, secretion, and degranulation. The immunological function can be independently altered by all these biochemical mediators released into the system. As an immunosuppressant, cortisol majorly contribute to T-helper cell responses in two ways (a) by suppressing the production of Type 1 helper (Th1) cell's major inducer, IL-12 (b) by enhancing the production of Th2 cytokines (IL-4, 10 & 13), which in turn boosts Th2 functions (65). Consequently, cortisol inhibits the macrophage-antigen presentation, lymphocyte proliferation, differentiation and overall dysregulation of the immune system occurs. Prolonged stress-related stimulation of the HPA suppress both immune and inflammatory responses and biological adjustments occur (43).

(b) Behavioural changes

Allostatic load reflects the influence of social circumstances and stressful life experiences, as well as behaviours, such as smoking, diet, exercise and alcohol consumption, which have been shown to largely contribute to the allostatic load construct. Indeed, health behaviours are well-known risk factors for periodontal disease and several other health conditions. However, while stress has been shown to correlate with poor health behaviours, some would argue that the role of behaviour in disease has been overemphasized, and that they are rather mediators of the psychosocial environment in which people live, rather than causals themselves. Social and living conditions generating psychosocial stressors and material constraints determine whether individuals' uptake harmful behaviour and whether they possess the necessary resources and motivation to care for their oral and overall health. Related to this is the link between the social environment and self-perceived health and health locus of control, which in turn affects one' s ability to change harmful behaviours (26, 55).

Furthermore, as the association between stress and periodontal disease needs to be clarified, prospective studies should take health behaviours into consideration to determine their contribution to the stress-periodontal disease relationship (20).

Allostatic load and periodontal diseases

A number of studies have examined the association between allostatic load, and specific biological markers of stress on one hand and periodontal diseases on the other. Bakri et al (2), using longitudinal data, found that patients with stress indicated by CRP and PSS at baseline had worse periodontal outcomes. The study was hindered by having a small sample size. Another study used a longitudinal design to examine the relationship among socioeconomic position, CRP as a marker of stress and periodontitis. However, both CRP and periodontitis were assessed at the same time point (6). Almost all other studies used either case-control or cross-sectional data. An association between salivary cortisol, interleukin-1β, interleukin-6 and periodontitis was demonstrated in a number of studies (4) (30) (45) (17) (27) (7). It is worth noting here that salivary cortisol is a marker of acute stress, hence it is difficult to verify a potential causal relationship with periodontal disease. Two known studies used a combined variable of different biological markers as indicators of Allostatic load, using data from different waves of the National Health and Examination Survey (NHANES). Sabbah et al (59) used an aggregate variable of seven biomarkers of Allostatic load, namely CRP, Fibrinogen, high blood pressure, waist circumference, Triglycerides, plasma glucose and HDL-Cholesterol to assess whether stress indicated by Allostatic load mediates the relationship between socioeconomic conditions and each of periodontal and ischemic heart diseases. The authors found an association between allostatic load and each of the conditions and argued that biological markers of stress possibly mediate the association between socioeconomic position and these health outcomes. Similarly, Borrell et al (3) argued that a combined variable of Allostatic load which included blood pressure, BMI, glycated haemoglobin, triglycerides level, C-reactive protein, homocysteine level, total cholesterol level, albumin, and creatinine, explains ethnic inequalities in periodontal diseases. Although these two studies used objective indicators of stress (Allostatic load), and used a large nationally representative samples of USA population, but their conclusions do not support temporality.

The role of stress reactivity and coping

It is not surprising that different studies used Allostatic load to explain socioeconomic and ethnic inequalities in periodontal in diseases. Indeed, studies on stress reactivity suggested that there are variations in response to acute and chronic stressors which are mostly influenced by employment status, education, social isolation, loneliness, effort-reward imbalance and belonging to ethnic minority (19) (35) (5). Individuals at the top of the social hierarchy are more likely to cope with stressful situation as they have more control over their lives and have the opportunity to engage in leisure activities to cope with daily stressors. On the other hand, those at the lower end of the social hierarchy are subjective to more frequent stressful situations, have fewer opportunities to engage in healthy activities that would help cope with stress, on the contrary they are more likely to engage in unhealthy behaviours such as smoking, binge drinking and comfort eating as a coping mechanism.

Personalized periodontics and Allostatic load

Categorising the patients into specific risk groups has been adopted in medicine and dentistry for years. However, with advances in medical sciences and laboratory investigation, and the ease of access to knowledge by healthcare providers and patients through the internet, there is higher demands for personalised dentistry and periodontics (75, 74) (62). The use of biomarkers of stress either individually or as a combined indicator of Allostatic load represent

an opportunity to tailor periodontal intervention to individual patients based on more complex and objective markers of risk. Undoubtedly, this will improve treatment outcomes and help contain the cost of periodontal treatment. Furthermore, given the patterns of regular dental visits in most industrialised countries, understanding allostatic load and its role in periodontal diseases and in other chronic conditions such as cardiovascular disease could enable dentists identify and refer patients at risk of other chronic conditions, and would help the integration of dentistry with other health specialities. Finally, the use of Allostatic load as a risk marker of periodontal diseases and cardiovascular diseases could also be beneficial for health promotion policies intending to tackle multiple health outcomes by addressing the common risk factors.

Opportunities for future research

Almost all the studies that examined the relationship between Allostatic load and oral health (67) (41, 59) (3) could not establish a causal relationship or temporality as they used cross-sectional data. Given the cost and difficulty of collecting repeated measures of Allostatic load and periodontal diseases, these cross-sectional data were the best available options. However, considering the potential benefit of establishing Allostatic load as a causal risk factor for periodontitis, researchers and funding agencies should work on developing longitudinal and intervention studies with adequate sample size to establish or refute Allostatic load/ periodontal diseases relationship.

Conclusions

In this narrative review several studies that examined the relationship between stress assessed by subjective instruments, and biological markers of stress, particularly Allostatic load, and periodontal diseases. Despite the methodological limitations of the studies that addressed this important relationship, there is a clear and plausible indication of a strong role of stress in periodontal diseases. The reviewed studies have also highlighted a number of biological indicators of Allostatic load which were collectively associated with periodontal disease. The review has also demonstrated the link among socioeconomic position stress/ Allostatic load and periodontal diseases highlighting a possible mediating role of stress in oral health inequalities. Finally, identifying biomarkers of stress could also help in establishing personalised periodontics.

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Table 1: Self-reported and structured interviews used to assess in relation to periodontal disease

Study ID	Instrument	Assessment method	Components	Measurement focus
Green et al., 1986 (21)	Life Experiences Survey (LES) (60)	Normative - Structured interview	Section 1 (47 items) explore life changes in a wide variety of situations and Section 2 (10 items) used among students	Major life events in the past year
Genco et al, 1998 (16)	(a) Life event scale – adaptation from Psychiatric epidemiology research interview (PERI) (13)	Subjective - questionnaire	Personal relationships (7 items), childbirth (8 items), work (9 items), finances (8 items), health and illness (7 items), crime and legal matters (8 items), residential and household events (7 items), and education (5 items) for 102 life events	Life events, including their perceived controllability and impact
	(b) Measures of Chronic Stress (Daily Strains) (51)	Subjective - questionnaire	Coping response items in marriage, parenting, household economics and occupation (84 items)	Coping responses in different role areas: spouse, parent, worker, and financial manager.
Hilgert et al 2006 (27)	Lipp's Stress Symptoms for Adults Inventory -LISS (38)	Subjective - questionnaire	Three sections dealing with the four phases of stress. (1) alarm, (2) resistance & near-exhaustion (3) exhaustion	Identify the phase of the stress process and physical/ psychological dimension of stress
Park et al., 2016 (49)	The Center for Epidemiological Studies-Depression scale (CES-D) (54)	Subjective - questionnaire	A 20-item measure that asks caregivers to rate affective, cognitive, behavioural and somatic symptoms within the previous seven days	Perceived stress, and pregnancy stress.
Fenoll et al , 2017 (15)	Depression, Anxiety, and Stress Scale (DASS) (37)	Subjective - questionnaire	21 scale with 7 item per scale measure related negative emotional states of depression, anxiety and tension/stress	Emphasises the links between the relatively enduring state of anxiety/ stress and the acute response of fear
Rosania et al 2009 (56)	Derogatis Stress Profile (DSP) (12)	Normative	77 items, seven (7) items for each of the 11 primary dimensions including "vocational environment, domestic environment, health environment, time pressure, driven behaviour, attitude posture, relaxation potential, role definition, hostility, anxiety, and depression"	Stimulus, response and interactional elements of stress
Solis et al 2004 (68)	Life Events Scale modified by Savoia (29, 61)	Subjective	List of 43 life-events related to "work, lack of social support, family, environmental changes, personal difficulties and financial strain"	Life events in the past year

Table 2: Primary and secondary markers of Allostatic load

Stress biomarkers	System	Biomarker
Primary markers	Neuroendocrine	Epinepherine, Norepinephrerine, Dopamine, salivary Cortisol, hair Cortisol, Noradrenaline, Dehydroepiandrosterone (DHEAS), aldosterone
Secondary outcomes	Immunological biomarkers	Interleukin-6, tumour necrosis Factoralpha, C-reactive protein (CRP), Fibrinogen, insulin-like growth factor-1 (IGF-1)
	Metabolic biomarkers	HDL and LDL Cholesterol, Triglycerides, Glucosylated Hemoglobin, Plasma Glucose, glucose insulin, Albumin, Creatinine, Homocysteine
	Cardiovascular and respiratory	Systolic blood pressure, Diastolic blood pressure, peak expiratory flow, heart rate/pulse
	Anthropometric	Waist-to-hip ratio, waist circumference, body mass index (BMI)